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PATENT APPLICATION
Attorney's Docket No.: MIT-7762
Expedited Procedure under 37 C.F.R. 1.116
Examining Group 1618

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Shuguang Zhang, Alexander Rich, Lin Yan and George Whitesides		
Application No.:	08/882,415	Group:	1618
Filed:	June 25, 1997	Examiner:	M. Garcia
For:	SELF-ASSEMBLING PEPTIDE SURFACES FOR CELL PATTERNING AND INTERACTIONS		

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CERTIFICATE OF MAILING

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BRIEF ON APPEAL

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Sir:

This Brief On Appeal is submitted to appeal the final rejection of the above-referenced application, which was mailed from the U.S. Patent and Trademark Office on March 30, 1999. A Notice of Appeal was mailed to the USPTO on August 30, 1999 and received on September 1, 1999.

A four-month extension of time for submission of this Brief is requested. A Petition for Extension of Time, the appropriate extension fees, and the fee for the filing of this Brief are enclosed.

Each of the requirements set forth in 37 C.F.R. § 1.192(c) follow under separate headings.

I. REAL PARTIES IN INTEREST

The real parties of interest are the Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139 and The President and Fellows of Harvard College, 124 Mount Auburn Street, Cambridge, Massachusetts 02138-5701.

II. RELATED APPEALS AND INTERFERENCES

The undersigned Attorney is not aware of any related appeals or interferences which directly affect or are directly affected by or have a bearing on the Board's decision in this pending Appeal.

III. STATUS OF CLAIMS

The application was filed with Claims 1-21. On July 6, 1998, the Examiner made a telephone Restriction Requirement and Applicants provisionally elected the claims of Group I, Claims 1-19. This provisional election was subsequently affirmed by Applicants in an Amendment mailed to the USPTO on January 8, 1999. In addition, original Claims 6, 9, 11 and 13 were amended in the Amendment mailed on January 8, 1999.

These claims were finally rejected in an Office Action mailed from the USPTO on March 30, 1999. Appellant submitted an Amendment After Final on August 30, 1999, pursuant to suggestions made by the Examiner in a telephonic interview on August 4, 1999, but the Examiner refused entry of these amendments in an Action mailed from the USPTO on December 2, 1999.

The pending claims, which are under final rejection, are presented in the Appendix to this Brief.

IV. STATUS OF AMENDMENTS

As mentioned above, Appellants' Amendment After Final was not entered. Further, in the Action of December 2, 1999, it was not indicated that this Amendment would be entered upon the filing of a Notice of Appeal and Appeal Brief. Thus, there have been no amendments to the claims since the final rejection.

V. SUMMARY OF THE INVENTION

Appellants' claimed invention is directed to a composition of matter comprising a self-assembled monolayer of peptides assembled on a solid support in a predetermined pattern and methods of making the same. The peptides are bound directly to the solid support through a terminal amino acid (see Claims and page 3, lines 1-5 and page 5, lines 12-17 of the Specification). Appellants' composition of matter does not include compositions of matter wherein peptides are not assembled in a predetermined pattern but instead are randomly or substantially homogeneously distributed over a solid support (see page 12, lines 16-20 of the Specification).

VI. ISSUES

1. Whether the rejection of Claims 1-17 under 35 U.S.C. 102 as being anticipated by the teachings of the Wang *et al.* Abstract, **Chemical Abstracts**, Vol. 125, Abstract No. 257089b (hereinafter "Wang Abstract") is proper; and

2. Whether the rejection of Claims 18 and 19 under 35 U.S.C. 103 as being unpatentable over the Wang Abstract in view of Kumar *et al.*, U.S. Patent 5,512,131 (hereinafter "Kumar '131") is proper.

VII. GROUPING OF CLAIMS

With respect to the issues to be decided, the claims stand or fall together.

VIII. APPELLANTS' ARGUMENTS

1. Anticipation Under § 102

A legally proper rejection under § 102 requires that the reference relied upon describes all the elements and limitations of the claims in a single prior art reference. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2nd, 1001, 1010 (CAFC 1991). The Wang Abstract fails to teach at least two limitations of Appellants' claims.

Initially, although the Wang Abstract discloses a layer of peptides on a solid surface, it does not teach that the peptides are "bound directly to said solid support through a terminal amino acid". Clearly, it teaches just the opposite by teaching that an ethylene central linker, $(CH_2)_2$, is employed to link the terminal amino group of the peptide to a terminal reactive thiol (SH) group for linking the peptide to the solid surface. See Wang Abstract, lines 12-13 and particularly the peptide-ethylene-thiol formula presented at line 15. In contrast, Appellants' peptide monolayers are attached to the solid support directly. See page 3, lines 1-5; page 5, lines 12-17 of the Specification; and claim language.

Further, the peptide layers of the Wang Abstract are not distributed on the surface of the solid support "in a predetermined pattern". A "predetermined" pattern is a pattern that is decided or established in advance. See **The American Heritage Dictionary**, Second College Edition, page 975 (1985). Not only does the Wang Abstract fail to teach a predetermined pattern, it fails to teach any pattern for the deposited peptides.

At times, it appears that the Examiner has confused the phrase from the Wang Abstract "Well-ordered protein assemblies" with a pattern of deposition. The term "Well-ordered" refers solely to the protein structure and not to any pattern on the substrate.

Since there seemed to be some confusion on the Examiner's part in regard to both limitations suggested above, Appellants obtained a copy of the full Wang *et al.* reference. This is Wang *et al.*, *Mat. Res. Soc. Symp. Proc. 414:17* (1996) (hereinafter "Wang Paper"). The Wang

Paper teaches the synthesis of two peptides which are covalently bound to a thioethyl group which can bind to a solid support. The two peptides have the following sequences (wherein "βA" refers to β-alanine):

$GRGD(\beta A)_3Y\text{-}NH(CH_2)_2SH$; and
$(\beta A)_6\text{-}NH(CH_2)_2SH$.

Three peptide monolayers were made by exposing a gold coated surface to a solution of the thioethyl modified peptides (see Exhibit A, p. 18, paragraph 1). The first Monolayer was composed of $GRGD(\beta A)_3Y\text{-}NH(CH_2)_2SH$, the second Monolayer was composed of $(\beta A)_6\text{-}NH(CH_2)_2SH$ and the third Monolayer was composed of a mixture of both peptides. The monolayers of peptides were then characterized by atomic force microscopy.

Monolayers prepared using peptide $(\beta A)_6\text{-}NH(CH_2)_2SH$ alone had a homogeneous, closely packed surface (see Exhibit A, page 19, lines 15-21). The peptide chains aligned in a β-sheet structure. It is this β-sheet structure which the phrase "[w]ell-ordered protein assemblies . . ." refers to in the abstract of Wang *et al.* It does not refer to the distribution of peptides on the surface in a predetermined pattern.

Monolayers prepared using peptide $GRGD(\beta A)_3Y\text{-}NH(CH_2)_2SH$ alone had islands of protein deposits of random size and location (see Exhibit A, page 19, lines 21-23 and Figure 2 on page 20).

Monolayers prepared using a 1:1 mixture of both peptides had surfaces which combined the features of monolayers prepared from each peptide alone (see Exhibit A, p. 19, lines 23-25).

In summary, in regard to the peptide layers deposited by Wang *et al.*, these were either homogeneous layers or islands of random size and location. These are the antitheses of a "predetermined pattern" and are expressly excluded from Appellants' definition of a predetermined pattern. See page 12, lines 13-20 of Appellants' Specification.

The Wang Paper also corroborates the fact that the peptides of Wang *et al.* are bound to the solid surface through a thioethyl group and are not bound directly to the support.

IX. NON-OBVIOUSNESS UNDER § 103

As discussed above, the Wang Abstract, and for that matter, the Wang Paper, are teachings away from Appellants' claimed invention rather than suggestions of it. The teachings of Kumar '131 are not properly combinable with those of the Wang Abstract, and the Examiner has supplied no reason why these should be combined. Certainly, the teachings of Kumar '131 do not overcome the teachings away of the Wang Abstract and the Wang Paper.

CONCLUSIONS

It is respectfully requested that the final rejection of the above-referenced application is legally improper and should be reversed.

Respectfully submitted,

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APPENDIX

CLAIMS

(per Amendment A filed January 8, 1999)

1. A composition of matter comprising a solid support and a self-assembled monolayer of linear peptides wherein said peptides bound directly to said solid support through a terminal amino acid in a predetermined pattern.

2. The composition of matter according to Claim 1 wherein said solid support is a metal.

3. The composition of matter according to Claim 2 wherein said metal is selected from the group consisting of gold, copper, nickel, zinc and silver.

4. The composition of matter according to Claim 1 wherein said solid support is selected from the group consisting of silica and glass.

5. The composition of matter according to Claim 1 wherein said solid support has two or more different peptides bonded thereon.

6. (Amended) The composition of matter according to Claim 1 wherein said peptide comprises a terminal reactive group, a central linker and a presenting group selected from the group consisting of peptides, antigens, antibodies, antibody fragments, cellular adhesion motifs, high chain alkyls, hydrophobically blocked amino acids and ligands.

7. The composition of matter according to Claim 6 wherein the peptides are extended beta strands.

8. The composition of matter according to Claim 6 wherein said terminal reactive group is a functional group pendant from a side chain, the amino or the carboxy group of the terminal amino acid of the peptide.

9. (Amended) The composition of matter according to Claim 8 wherein the terminal reactive group is selected from the group consisting of a hydroxy, thiol, carboxy, amino, amido, imide and guanidino group.

10. The composition of matter according to Claim 9 wherein the peptide comprises a terminal amino acid selected from the group consisting of serine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, histidine and arginine.

11. (Amended) The composition of matter according to Claim 10 wherein said terminal amino acid is selected from the group consisting of serine, aspartic acid, glutamic acid and cysteine.

12. The composition of matter according to Claim 10 wherein said central linker comprises between about 2 to about 50 amino acids.

13. (Amended) The composition of matter according to Claim 12 wherein said central linker is selected from the group consisting of a oligoglycine and oligoalanine.

14. The composition of matter according to Claim 13 wherein said presenting moiety is a peptide that possesses an affinity to a target molecule.

15. The composition of matter according to Claim 14 wherein the target molecule is a cell surface protein and the presenting group is selected from the group consisting of a ligand, an antibody or an antibody fragment which binds specifically to the cell surface protein.

16. A composition of matter comprising a solid support and a self-assembled monolayer of linear peptides wherein said peptides bound directly to said solid support through a terminal amino acid in a predetermined pattern, the peptide further being characterized by the formula:

$$X\text{-}(CH_2)_n\text{-}CH(NH_2)CO(AA)_m\text{-}L$$

or

$$X\text{-}(CH_2)_n\text{-}CH(COOH)NH(AA)_m\text{-}L$$

wherein X is H, alkyl, alkoxy, alkylthio or dialkylamine, thiol, hydroxy, amino or carboxy;
AA is, independently, the same or different, naturally-occurring or non-naturally-occurring amino acid;
L is a group which binds specifically or non-specifically to a target;
n is zero or an integer between 1 to about 5; and
m is an integer of at least about 2.

17. A self-assembled monolayer of a chemical reactive moiety on a solid support, the improvement comprising linking said chemical reactive moiety to said solid support through one or more peptide linkages.

18. A method for manufacturing a composition of matter comprising a solid support and a self-assembled monolayer of linear peptides wherein said peptides bound directly to said solid support through a terminal amino acid in a predetermined pattern comprising the steps:

(a) contacting an elastomeric stamp characterized by a relief of said predetermined pattern with a solution containing a compound which can react with said solid support;

(b) contacting said stamp with a surface of said solid support under conditions suitable for the reaction between said compound and said solid surface, wherein said compound reacts with said solid support at points of contact between said stamp and said solid support, corresponding to the relief of said predetermined pattern;

(c) removing said stamp; and

(d) contacting said solid support with a solution containing said linear peptides under conditions suitable for the reaction of said peptide and said solid support.

19. A method for manufacturing a composition of matter comprising a solid support and a self-assembled monolayer of linear peptides wherein said peptides bound directly to said solid support through a terminal amino acid in a predetermined pattern comprising the steps:

(a) contacting an elastomeric stamp characterized by a relief of said predetermined pattern with a solution containing said linear peptide;

(b) contacting said stamp with a surface of said solid support under conditions suitable for the reaction between said linear peptide and said solid surface, wherein said linear peptide reacts with said solid support at points of contact between said stamp and said solid support, corresponding to the predetermined pattern; and

(c) removing said stamp.